Journal of Family Medicine

Open Access

Austin Publishing Group

Research Article

Are we Asleep at the Wheel in Diagnosing of Myeloma

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Received: July 20, 2020; **Accepted:** November 17, 2020; **Published:** November 24, 2020

Abstract

Multiple Myeloma (MM) is the abnormal proliferation of plasma cells in the bone marrow often resulting in debilitating symptoms ranging from ostealgia to pathological fractures from bone destruction. According to American Cancer Society, MM accounts for 1-2 % of cancers and approximately 17% of hematological malignancies in the United States each year [1]. Fifty percent of patients with symptomatic MM have three or more primary care visits before they are referred to a specialist, which is greater than any other cancer [2]. It has been shown that a delay in diagnosing multiple myeloma negatively impacts the clinical course of the disease and hence the outcome in patients. Patients with longer diagnostic intervals also experience shorter disease-free survival and more complications from treatment [3]. Early diagnosis of MM has been previously shown to help improve survival rate by timely and effective treatment. We performed a retrospective analysis to determine the average delay in diagnosis of MM from time patients have lab abnormalities related to their disease.

Keywords: Multiple myeloma

Background

Multiple Myeloma (MM) is a plasma cell neoplasm characterized by clonal proliferation of malignant plasma cells resulting in anemia, recurrent infections and renal failure and debilitating symptoms due to bone destruction. MM is the second most common hematological malignancy which accounts for 1-2 % of cancers.

The early symptoms of myeloma are most commonly fatigue and back pain, which are also common for benign conditions and therefore often results in delaying the diagnosis. Over fifty percent of patients with symptomatic MM have three or more primary care visits before they are referred to a specialist, which is greater than any other cancer [3]. In addition, many patients experience symptoms for months before seeking help. What's more disturbing is that even after seeing a primary care physicians with symptoms related to myeloma, the median time to diagnosis is over 100 days, with 25% of patients waiting longer than 8 month to make the diagnosis resulting in over five months from time of first symptom to date of diagnosis [4].

A delay in diagnosing MM results in severe morbidity, which include end organ damage such as renal failure, life threatening infections, pathological fractures and spinal cord compression. This often results in patients presenting with medical emergencies causing delays in delivering effective therapies. It has been shown that a delay in diagnosing multiple myeloma negatively impacts the clinical course of the disease and hence outcomes [5]. Patients with longer diagnostic intervals also experience shorter disease-free survival and more complications from treatment [1].

Over the past two decades the treatment landscape for MM has been transformed by the introduction of novel agents, which include immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies; which have resulted in a steady improvement in survival [6]. There has also been emerging evidence demonstrating a benefit to treating patients at an earlier phase of the disease, which is known as smoldering myeloma [7]. With more effective therapies and a shift in paradigm to earlier treatment, it's now more important than ever to not to delay the diagnosis of MM. Herein, we evaluated the time delay in diagnosis from when physicians first have evidence of lab abnormalities suggesting a diagnosis of MM.

Methods

This is a retrospective electronic chart review of all indexed newly diagnosed MM cases between 1/1/2014 through 12/31/2018 on bone marrow biopsy done at New York-Presbyterian Brooklyn Methodist Hospital (NYP BMH). NYP BMH is a Weill Cornell Medical College-affiliated hospital in Brooklyn, NY whose patient population includes privately insured, uninsured and Medicare/Medicaid. Data abstraction from the Electronic Medical Record (EMR) was uniform and involved baseline characteristics including age, gender and race. International Classification of Diseases (ICD)-10-CM code (C90.00) was used for extraction of data which identified 492 patients.

313 patient charts were reviewed and patients with MGUS or a prior diagnosis of multiple myeloma were excluded, leaving a total of 104 patients in the final study who were newly diagnosed with MM at NYP-BMH. The hospital EMR was utilized to collect pertinent labs on these patients. These patients either were discharged from the emergency room or were admitted.

The Complete Blood Count (CBC) and Basic Metabolic Panel (BMP) recorded on the EMR before and at the time of diagnosis were reviewed. We calculated the number of days between the dates of the first abnormal laboratory value seen on bloodwork for a myeloma related sign (at least 90 days prior to diagnosis) to the date of bone marrow biopsy that confirmed the diagnosis. The inclusion criteria included anemia defined as hemoglobin <12gm/dl, hypercalcemia defined by corrected calcium >10, kidney dysfunction with a creatinine >1.5 and total protein >8. Cytogenetic characteristics of patients diagnosed with MM were also reviewed.

Citation: Ghalehsari N, Kancharla P, Nimkar NS, Mazloom A, Ashraf F, Singh A, et al. Are we Asleep at the Wheel in Diagnosing of Myeloma. J Fam Med. 2020; 7(9): 1230.

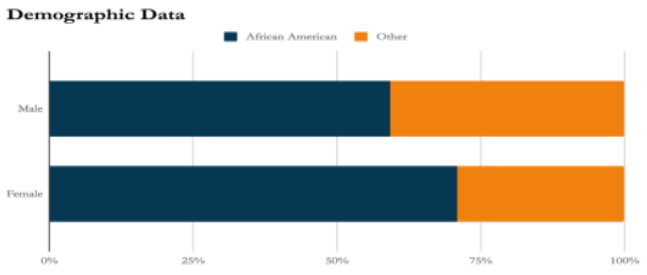

Figure 1: Demographic data.

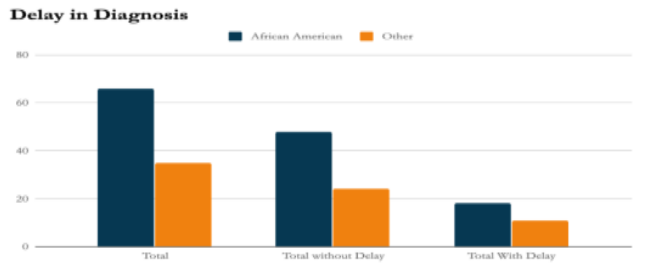

Figure 2: Delay in diagnosis.

Results

There were 104 patients included in the study with an average age of 69. Of these patients, 44% were male and 56% were female (Figure 1). 64% of these patients were African American and the rest were either Caucasian, Asian or others (Figure 2). Of the 104 patients with newly diagnosed MM, 75 patients were diagnosed within 90 days of the first abnormal lab value recorded in our Electronic Medical Record (EMR). This means that within 90 days of initial abnormal lab finding in these patients, a bone marrow was performed and MM diagnosis was made. Twenty-nine patients (28%) had a delay in diagnosis at least 90 days with a mean delay of 41 months. Eighteen of these patients (62%) with delay in diagnosis were African American.

Anemia was the most common abnormal lab finding all the twenty-nine patients had a documented anemia at least 90 days prior to diagnosis of myeloma with hemoglobin value ranging from 5.8 to 12.0. Average lab findings at the time of diagnosis in patients in both with and without delay in diagnosis are reported in (Table 1). Isolated anemia without other lab abnormalities was present in 11 of these patients. The rest of these patients had presented with anemia and another lab abnormality, as follows: there were four patients with anemia and elevated creatinine with an average delay of 23 months. Five patients had anemia and elevated calcium with an average delay of 21 months. Nine patients had anemia and elevated total protein with an average delay of 38 months (Figure 3). Finally, our data showed that 6 out of the 29 patients with delay in diagnosis (29%) demonstrated complex cytogenetics. Four out of these six patients (67%) were African American.

Discussion

There is a growing body of literature about the delay in diagnosis of MM. Most studies to date have focused on intervals from when patients first experienced subjective symptoms to time of MM

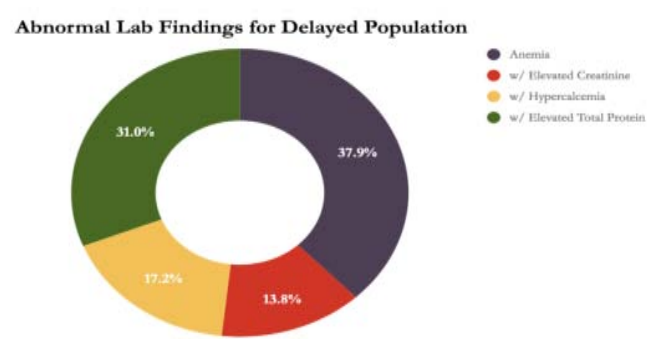

Figure 3: Average lab findings for delayed population.

Table 1: Average lab findings in both groups.

Lab findings	Average in group without delay	Average in group with delay
Hemoglobin	10.2	9.9
Total Protein	8.9	8.4
Creatinine	2	1.27
Calcium	10.2	8.8

diagnosis. In this report, we evaluated the time from when there was objective lab data available to the clinician, which should have prompted a workup for myeloma and instead was overlooked. We found that 28% of patients had a delay in their diagnosis by at least 90 days with a mean delay of 41 months after their physician had lab evidence warranting a workup for MM. Isolated anemia was the largest subset of patients in the delayed diagnosis group (37.9%), which suggests that clinicians are less likely to raise the suspicion for multiple myeloma when evaluating anemia without other lab abnormalities. Nine patients in our cohort had anemia and an elevated serum total protein (31%) and this group had the longest delay in diagnosis with an average of 38 months. Elevated protein is a result of a clonal paraproteinemia and although MM is universally preceded by a prolonged premalignant stage of MGUS [8]. All patients in our cohort had anemia, which suggests that they all had already progressed to MM. Although a bone marrow, biopsy is required to confirm the diagnosis of MM, a simple blood test panel checking for a paraprotein by electrophoresis and serum free light chains that has almost 100% sensitivity can help a clinician determine if further workup for MM warranted.

Koshiaris et al recently reported a meta-analysis quantifying the duration of each step in the diagnostic pathway of MM and found that the median time to diagnosis was 163 days [9]. When breaking down the time of first symptom to diagnosis by intervals; the longest delay was from the time of first presentation to diagnosis. This is consistent with our findings that the delay in MM diagnosis often occurs even after physicians are presented with information that should prompt the workup of myeloma. The delay in diagnosis of MM has severe consequences by causing pathological fractures, chronic pain syndromes and renal failure often requiring hemodialysis. Moreover, patients who had a delay of MM diagnosis are more likely to have advanced stage with worse outcomes and a reduced disease-free survival [10].

The incidence of MM is known to be higher amongst African

Americans [11]. In our cohort, the majority of patients with a delay in diagnosis were African Americans from areas with low known low socioeconomic populations. Lack of access to medical care and frequent follow up may have contributed to delays in this population. Primary care physicians are often the first point of contact when patients present with symptoms related to MM and provide a vital opportunity for general practitioners to start the appropriate workup. The challenge with MM, is that patients often present with non-specific symptoms such as fatigue and back pain which are common benign findings in primary care and do not provide by itself a significant predictive value to initiate a workup for MM [12]. However, when combining these symptoms with common lab abnormalities, one can develop an algorithm to identify high-risk patients. In the era of electronic medical records, there is an opportunity to use databases and analytics to develop clinical risk prediction models to aid clinicians in identifying patients who should get further workup for possible MM. Our work demonstrates the need for more awareness and education among primary care providers about the evaluation of lab abnormalities and symptoms related to myeloma, which should help lead to earlier diagnosis and better outcomes.

Conclusion

In the current era where we have effective therapies for MM it is now more important than ever to avoid a delay in diagnosis. We demonstrate that 28% of patients receiving care at an Urban Teaching Hospital had at least a 90-day delay in their diagnosis of MM. Our cohort consisted of 64% African Americans, suggesting that minorities are more commonly affected by this.

Unlike some other types of malignancies, there have been no screening modalities described in hematological malignancies such as multiple myeloma. There is a need for more awareness amongst clinicians to consider the diagnosis of MM in the workup of anemia. Larger retrospective or prospective studies are needed to search for possible delays in diagnosis of MM. Anemia and other end organ impairments should be used as screening tools for this malignancy.

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